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ASTRAZENECA R&D BOSTON
35 GATEHOUSE DRIVE
WALTHAM, MA 02451-1215

EXAMINER	
HA, JULIE	

ART UNIT	PAPER NUMBER
1654	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/569,583	GALLAGHER, NEIL	
	Examiner	Art Unit	
	Julie Ha	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 September 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,9,11 and 24-28* is/are pending in the application.

4a) Of the above claim(s) *24-26 and 28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,9,11 and 27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Amendment after Non-final filed on September 12, 2007 is acknowledged. Claims 1, 3-8, 10 and 12-23 have been cancelled. Claims 2, 9, 11 and 24-28 are pending in this office action. Applicant elected without traverse of Group II (claims 2 and 9) drawn to a combination comprising N-(3-methoxy-5-methylpyrazin-2-yl)-2-(4-[1,3,4-oxadiazol-2-yl]phenyl)pyridine-3-sulphonamide and a bisphosphonate, and species election of pamidronic acid, in the reply filed on January 12, 2007. The restriction requirement is deemed proper and made FINAL. Claims 24-26 and 28 have been withdrawn from consideration, as being drawn to non-elected species. Claims 2, 9, 11 and 27 are examined on the merits in this application.

Withdrawn Objections

1. Objection to specification is hereby withdrawn due to Applicant's amendments.

Maintained Rejection-35 U.S.C. 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 2, 9, 11 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Janus et al (PG Pub 2002/0055457) in view of Curwen et al (Poster EORTC-NCI-AACR, 2002), Nelson et al (BJU International, 2000, 85(suppl 2), 45-48) and Walczak et al (Expert Opin. Investig. Drugs, 2002).

4. The instant claims are drawn to a combination comprising N-(3-methoxy-5-methylpyrazin-2-yl)-2-(4-[1,3,4-oxadiazol-2-yl)phenyl)pyridine-3-sulfonamide and a bisphosphonate (pamidronic acid or a pharmaceutically acceptable salt thereof). The claims are additionally drawn to a pharmaceutical composition comprising a combination in association with a pharmaceutically acceptable diluent or carrier.

5. Janus et al (PG Pub 2002/0055457) discloses a method of inhibition of bond metastases including in cancer patients an effective amount of an endothelin ET-A receptor antagonist (see claim 1). The reference further teaches that the primary cancer is prostate cancer (see claim 4). Furthermore, the reference teaches that the method comprises administration of a therapeutic agent, bisphosphonate (see claim 9). The reference teaches that therapeutic agent (bisphosphonate) addition impedes net bone loss (see claim 8). Additionally, the reference teaches the pharmaceutical formulations, the compounds may be administered orally, buccally, parenterally, sublingually, by inhalation spray, rectally, or topically in dosage unit formulations containing conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles

(see paragraphs [0115] and [0117]). This reads on claims 2 and 11. The difference between the reference and the instant claims is that the reference does not teach N-(3-methoxy-5-methylpyrazin-2-yl)-2-(4-[1,3,4-oxadiazol-2-yl]phenyl)pyridine-3-sulphonamide.

6. However, Curwen et al (Poster, 2002) teach that ZD4054 (N-(3-methoxy-5-methylpyrazin-2-yl)-2-(4-[1,3,4-oxadiazol-2-yl]phenyl)pyridine-3-sulphonamide), a specific endothelin A receptor antagonist has utility in prostate cancer and metastatic bone disease (see poster, Figure 1, Results and Discussion). The reference further teaches that in *in vitro* studies, ZD4054 is a high-affinity ligand for the human ET_A receptor, with a pIC_{50} value of 8.27, while ZD4054 had no measurable affinity for the ET_B receptor (see Results, In vitro radioligand binding studies). Additionally, the reference teaches that ZD4054 is a potent ETA receptor antagonist in vivo, producing a dose-related response (see Figure 2a and Results, Intravenous antagonist potency).

7. Nelson et al (BJU International, 2000) teach that the endothelin (ETs) are identical in all mammals and many higher vertebrates; the ET receptors are also very similar (see p. 45, left column, 2nd paragraph). Additionally, the reference teaches that every prostate cancer cell line tested produces ET-1 mRNA and protein (see p.45, right column, 2nd paragraph). Furthermore, the reference teaches that using a selective ET_A receptor antagonist, the abdominal constrictor response of mice to ET-1 was completely inhibited (see pp. 46, right bottom paragraph and p. 47, top left paragraph).

8. Walczak et al (Expert Opin. Investig. Drugs, 2002) teach that men with hormone-independent prostate cancer are at risk for skeletal morbidity (see p. 1742, 1st 2 lines of

4. Bone-targeted therapy). The reference further teaches that bisphosphonates exert their action by inducing apoptosis of osteoclasts. Bisphosphonates have demonstrated in vitro inhibitory effect on breast and prostate cancer cell adhesion to bone, and a direct cellular effect in inhibiting tumor cell invasion and proteolytic activity of matrix metalloproteinases. Pamidronate disodium and zoledronic acid have also shown in vitro inhibition of prostate cancer cell growth (see p. 1742, section 4.1).

9. Therefore, it would have been obvious to the ordinary skilled in the art to combine the bisphosphonate and endothelin receptor antagonist. There is a reasonable expectation of success, since bisphosphonate is used in treatment of prostate cancer and endothelin receptor antagonist (ZD4054) is used in treatment of prostate cancer, thus combining the two into a combination compound would show at least an additive effect. Additionally, the ordinary skilled artisans would be motivated to combine the teachings of the prior arts because Curwen et al teach that ZD4054 is a high-affinity ligand for the human ET_A receptor, with a pIC_{50} value of 8.27, while ZD4054 had no measurable affinity for the ET_B receptor. Furthermore, Janus et al teach that bisphosphonate addition impedes bone loss (see claim 8). Therefore, since ZD4054 is selective for ET_A receptor, one would expect it to be active.

Response to Applicant's Arguments

10. Applicant argues that the Examiner had to combine the teachings of four references to arrive at the stated conclusion. Furthermore, Applicant argues that three basic criteria must be met for prima facie case of obviousness: 1) there must be some

suggestion or motivation, either in the references themselves or in the knowledge available to ordinary skill in the art; 2) there must be a reasonable expectation of success; and 3) the prior art reference must teach or suggest all the claimed invention. Additionally, Applicant argues that the beneficial results (i.e., no bone metastases) appear to go beyond the "additive effect" discussed by the Examiner and thus provide further support of the patentability of the present invention.

11. Applicant's arguments have been considered but have not been found persuasive because the prior arts combined the prima facie obviousness of the instant application. In response to applicant's argument that the examiner has combined an excessive number of references, reliance on a large number of references in a rejection does not, without more, weigh against the obviousness of the claimed invention. See *In re Gorman*, 933 F.2d 982, 18 USPQ2d 1885 (Fed. Cir. 1991). Janus et al teach a method of inhibition of bone metastases by administering an effective amount of an endothelin ET-A receptor antagonist (see claim 1). Janus et al also teaches that the method comprises administration of a therapeutic agent, bisphosphonate (see claim 9), and this addition impedes net bone loss (see claim 8) in treating prostate cancer. Curwen et al teach that ZD4054, (N-(3-methoxy-5-methylpyrazin-2-yl)-2-(4-[1,3,4-oxadiazol-2-yl]phenyl)pyridine-3-sulphonamide), is a specific endothelin A receptor antagonist and has utility in prostate cancer and metastatic bone disease. Nelson reference teaches that the endothelin (ETs) are identical in all mammals and many higher vertebrates, and the ET receptors are also very similar, and that every prostate cancer cell line tested produces ET-1 mRNA and protein, and that using a selective

ETA receptor antagonist, the abdominal constrictor response of mice to ET-1 was completely inhibited. Walczak et al teach that bisphosphonates exert their action by inducing apoptosis of osteoclasts, and have demonstrated in vitro inhibitory effect on breast and prostate cancer cell adhesion to bone, and a direct cellular effect in inhibiting tumor cell invasion and proteolytic activity of matrix metalloproteinases. Walczak reference teaches that pamidronate disodium and zoledronic acid have shown in vitro inhibition of prostate cancer cell growth. Therefore, it would have been obvious to combine the teachings of the prior arts to produce a pharmaceutical composition comprising (N-(3-methoxy-5-methylpyrazin-2-yl)-2-(4-[1,3,4-oxadiazol-2-yl]phenyl)pyridine-3-sulphonamide) and bisphosphonate (pamidronate), since Jauns et al show that ET-A receptor antagonist and bisphosphonate addition impedes net bone loss and is for treating prostate cancer, and other references show the activity of ET-A receptor antagonist against prostate cancer and metastatic bone disease. There is a reasonable expectation of success, since bisphosphonate is used in treatment of prostate cancer and endothelin receptor antagonist (ZD4054) is used in treatment of prostate cancer, therefore, combining the two into a combination compound would show at least an additive effect. Further, since ZD4054 is selective for ET-A receptor, and Janus et al disclosed that bisphosphonate addition impedes bone loss, there is a reasonable expectation that the addition of the two compounds into one composition would have an additive effect.

12. Furthermore, It has been held that under KSR that "obvious to try" may be an appropriate test under 103. The Supreme Court stated in KSR, When there is

motivation "to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103." *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727,_,82 USPQ2d 1385, 1397 (2007).

13. The "problem" facing those in the art was the use of ET/ET receptor antagonists alone or with a co-therapeutic agent for the treatment of prostate cancer and bone metastases, and there were a limited number of methodologies available to do so, for example, combination of compounds at different concentrations, combination of different co-therapeutic agent with ET-A receptor antagonist, and so on. The skilled artisan would have had reason to try these methodologies with the reasonable expectation that at least one would be successful. In this case, Janus et al teach ET-A receptor antagonist and the addition of bisphosphonate to treat prostate cancer and impede net bone loss; Curwen et al teach that ZD 4054 is a high affinity ligand for the human ET-A receptor and that it is a potent ET-A receptor antagonist in vivo; Nelson et al teach that ETs are identical in all mammals and many higher vertebrates, and that every prostate cancer cell line tested produced ET-1 mRNA and proteins, thus, must act the same; and Walczak et al teach that bisphosphonate exert their action by inducing apoptosis of osteoclasts, and have shown inhibitory effect on breast and prostate cancer cell adhesion to bone, and pamidronate and zoledronic acid have shown in vitro inhibition of prostate cancer cell growth. Because the prior arts teach that the ET-A

receptor antagonist and bisphosphonate can be combined together, and since (N-(3-methoxy-5-methylpyrazin-2-yl)-2-(4-[1,3,4-oxadiazol-2-yl]phenyl)pyridine-3-sulphonamide) and bisphosphonate (pamidronate and zoledronic acid) act to inhibit prostate cancer cell growth, treating prostate cancer using combination of (N-(3-methoxy-5-methylpyrazin-2-yl)-2-(4-[1,3,4-oxadiazol-2-yl]phenyl)pyridine-3-sulphonamide) and bisphosphonate (pamidronate or zoledronic acid) is a "the product not of innovation but of ordinary skill and common sense," leading to the conclusion that invention is not patentable as it would have been obvious.

Conclusion

14. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). No claims are allowed.

15. A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Julie Ha whose telephone number is 571-272-5982. The examiner can normally be reached on Mon-Fri, 8:00 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Julie Ha
Patent Examiner
AU 1654

10/16/09
ANISH GUPTA
PRIMARY EXAMINER